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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,557	05/02/2002	Dan L. Eaton	GNE.3230R1C39	9770

7590 10/19/2004
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EXAMINER

BLANCHARD, DAVID J

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 10/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/063,557	Applicant(s) EATON ET AL.	
	Examiner David J Blanchard	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 August 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 6 has been canceled.
Claim 1 has been amended.
2. Claims 1- 5 are pending and under examination.
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Inventorship

4. The request for the deletion of an inventor in this nonprovisional application under 37 CFR 1.48(b) is deficient because:

The request was not signed by a party set forth in 1.33(b) and the request does not acknowledge that the deleted inventor's invention is no longer being claimed in the instant application as required under 37 CFR 1.48(b)(1).

Objections/Rejections Withdrawn

5. The objection to the specification for containing embedded hyperlinks is withdrawn in view of the amendment to the specification.
6. The objection to the Oath/Declaration is withdrawn in view of Applicant's arguments.
7. The rejection of claims 1-6 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention is withdrawn in view of the amendments to the claims and Applicant's arguments.

8. The rejection of claims 1-2 and 4-6 under 35 U.S.C. 102(b) as being anticipated by Lal et al is withdrawn in view of Applicant's arguments and the instant claims deemed to be fully entitled to the priority date of PCT/US00/23328, i.e., 24 August 2000.

Response to Arguments

9. Claims 1-5 are rejected under 35 U.S.C 101 because the claimed invention is not supported by a specific and substantial asserted utility or a well-established utility is maintained.

The response filed 8/16/2004 has been carefully considered, but is deemed not to be persuasive. The response argues that the identification of the differential expression of the PRO polypeptide-encoding nucleic acid in more than one or more tumor tissues as compared to one or more normal tissues of the same type render the polypeptide as a useful target for diagnosis and treatment and in the majority of cases, gene expression correlates with levels of protein expression and submits the declaration of Dr. Grimaldi (Exhibit B) and the submitted declaration of Dr. Polakis (Exhibit C) states that it remains a central dogma that increased levels of mRNA are predictive of increased levels of protein and cites Orntoft et al, Hyman et al and Pollack et al for support (see pages 8-9 of the response). In response to this argument, the declarations and art cited by Applicant have been carefully considered but are deemed not to be

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persuasive. The Polakis declaration states that in 80% of the observations they have found that increases in the levels of a particular mRNA correlates with changes in the level of protein expressed from that mRNA in human tumor cells. In response to this argument, the examiner cited art in the 112 first rejection that supports that mRNA over-expression does not correlate with protein over-expression. Further, while the declaration may show a correlation between mRNA and protein over-expression in some cases, the references cited on page 9 of the response (Orntoft et al, Hyman et al and Pollack et al), only show mRNA overexpression relative to gene amplification and Applicant appears to have acknowledged this at the top of page 10 of the response. No evidence has been submitted that it is the norm rather than the exception that protein levels parallel gene expression in cancer cells. As evidenced by Gokman-Polar et al (Cancer Research, 2001, 61:1375-1381), the absence of any necessary correlation between increased mRNA levels and increased protein levels is made explicit by Gokman-Polar et al (Cancer Research, 2001, 61:1375-1381) who teaches "Quantitative reverse transcription-PCR analysis revealed that PKC mRNA levels do not directly correlate with PKC protein levels, indicating that PKC isoenzyme expression is likely regulated at the posttranscriptional/translational level" (see abstract). Gokman-Polar et al show in figures 6 and 7 that there is no increase in mRNA expression for any of the isoenzymes, while the protein is significantly overexpressed as shown by figures 4 and 5. Therefore, in view of the art cited by the examiner in the 112 first rejection and as evidenced by Gokman-Polar et al above it is not necessarily the norm that gene expression, or even transcription, parallels protein expression. Thus, in view of the

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totality of evidence, the skilled artisan would not assume that gene expression necessarily parallels or is predictive of protein expression, but would perform the experiment to verify it.

Finally, Applicant refers to the Ashkenazi declaration (Exhibit D), which argues that assuming *arguendo* that there is no correlation between gene expression and decreased protein expression for PRO1069, an antibody to a polypeptide encoded by a gene that is under-expressed in cancer would still have utility and identification of both gene and protein expression provide a more accurate tumor classification and hence better determination of suitable therapy. This has been fully considered but is not found to be sufficient to withdraw this rejection, since there is no indication that PRO1069 protein levels increase or stay the same. Further research would be required to determine PRO1069 protein levels in cancers showing gene amplification of PRO1069. Therefore, the asserted utility is not substantial as the real-world use has not been established and also is not specific because Applicant has not provided any objective evidence correlating the expression of the PRO1069 polypeptide with any particular disease state (e.g., kidney tumor). As the utility guideline materials note at page 5-6 (See: Federal Register: December 21, 1999 (volume 64, Number 244), revised guidelines for Utility), "Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed". Thus, the proposed use of the PRO1069 protein (and by extension the antibodies as claimed in this application) are simply starting points for further research and investigation into potential practical uses of the protein

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and antibodies. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field" and "a patent is not a hunting license" "[i]t is not a reward for the search, but compensation for its successful conclusion."

Therefore, the rejection under 35 U.S.C 101 is maintained.

10. The rejection of claims 1-5 under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention is maintained for the reasons above.

11. The rejection of claims 1-5 under 35 U.S.C. 112, first paragraph, because the claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

The response filed 8/16/04 has been carefully considered, but is deemed not to be persuasive. The response argues that the declarations and references discussed above make clear that mRNA does in fact coorelate with equivalent levels of polypeptide expression, and that the general understanding of those of skill in the art is

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that it is more likely than not that gene expression levels and protein expression levels are correlated and antibodies to the PRO1069 polypeptide have a specific and substantial use in the diagnosis and characterization of cancer cells. In response to this argument and as discussed above (see 35 U.S.C 101 rejection above, item #8), the totality of evidence (the art cited by Applicant and that made of record by the Examiner) only underscores the unpredictability in the art and the skilled artisan would not reasonably conclude that mRNA expression necessarily correlates with protein expression. Fu teach that levels of p53 protein expression do not correlate well with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia; Powell teach that mRNA levels for cytochrome P450 E1 did not correlate with the level of corresponding protein; Vallejo teach that no correlation was found between NRF-2 mRNA and protein levels; Lewin B (an instructional textbook) states "But having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription" (see page 847, right column) and Jang teach that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells. Again, while Applicant has provided evidence that for some genes, increased levels of a particular mRNA correlates with changes in the level of protein expressed from that mRNA, this only further underscores the unpredictability in the art. Given the totality of evidence, the skilled artisan would not accept that gene amplification of PRO1069 necessarily

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correlates with PRO1069 protein expression, but would perform the experiment to verify it. Therefore, in the absence of objective evidence that PRO1069 gene amplification correlates with PRO1069 protein expression correlated to a specific disease state (e.g., kidney tumor), the skilled artisan would not predictably know how to use antibodies that bind the PRO1069 protein (SEQ ID NO:50) for cancer therapy and diagnosis.

Applicant's arguments with respect to *Noelle v. Lederman* (355 F.3d 1343 (Fed Cir. 2004)) are not relevant to the instant rejection because the instant rejection was made under 35 U.S.C. 112, first paragraph, enablement, whereas the facts in *Noelle v. Lederman* are directed towards the written description requirement pursuant to 35 U.S.C. 112, first paragraph and not enablement.

Therefore, the rejection under 35 U.S.C. 112, first paragraph, enablement is maintained.

12. Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lal et al in view of Queen et al is maintained.

The response filed 8/16/04 has been carefully considered, but is deemed not to be persuasive. The response argues that the instant claims are entitled to the effective filing date of 24 August 2000 (i.e., PCT/US00/23328) and as this date is not more than one year prior to the effective filing date of the instant application, Lal et al is not prior art under 35 U.S.C. 103(a). In response to this argument, the publication date of Lal et

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al is 6 January 2000, which is at least 7 months prior to applicants effective filing date (8/24/2000) and thus, qualifies as prior art under 35 U.S.C. 103(a). Applicant is reminded that under 103(a), all that is required is that the invention was known or used by others in this country, or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent. Under 103(a), it is not required that the applied references be more than one year prior to the effective filing date of the instant application, i.e., 24 August 2000.

Therefore, the rejection of claims 1-5 under 35 U.S.C. 103(a) as being unpatentable over Lal et al in view of Queen et al is maintained.

Conclusions

13. No claim is allowed.


14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827



HARRY R. HELMS, PH.D
PRIMARY EXAMINER